# Elovl6 deficiency prevents diabetes in db/db mice by increasing β-cell mass and insulin secretory capacity

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## 論文の要旨
## Abstract of thesis


【背景・目的 Background/Purpose】

The elongation of very long-chain fatty acid (ELOVL) family member *Elovl6* is a microsomal enzyme involved in the elongation of saturated and monounsaturated FAs with 12, 14, and 16 carbons. Loss of *Elovl6* function reduces stearate (C18:0) and oleate (C18:1n-9) levels and increases palmitate (C16:0) and palmitoleate (C16:1n-7) levels.　In the previous study, it has been reported that mice with the targeted disruption of Elovl6 (*Elovl6*$^{-/-}$) were protected against the development of hepatic insulin resistance and deterioration of insulin secretory function of pancreatic β cells in animals fed a high-fat and high-sucrose diet, despite similar levels of hepatosteatosis and obesity between *Elovl6*-deficient and wild-type mice.These findings suggested that the vital role of alterations in FA composition by *Elovl6* deficiency extended beyond lipid accumulation and impacted insulin sensitivity and β-cell function. The author speculated that *Elovl6* inhibition could be a potential therapeutic approach in type 2 diabetes (T2D) treatment. The author would like to investigate about following points:

- To determine the effect of endogenous Elovl6 in leptin receptor –deficient *db/db* mice (*db/db: Elovl6-/-*)

- To determine whether beta-cell function and islet inflammation could be altered by changes in cellular FAs regulated by Elovl6

【対象と方法　Material and methods】

*Lepr*$^{db/+}$ (*db*/+) mice on a C57BL/KsJ background were purchased and the author crossed with *Elovl6*$^{-/-}$ mice (C57BL6J background) to obtain *db/+;Elovl6*$^{+/-}$ mice. *db/+;Elovl6*$^{+/-}$ mice were then crossed more than seven generations into the C57BL/KsJ background. Finally, double heterozygous male and female mice were bred to generate mice with the double mutation of *Lepr* and *Elovl6* (*db/db;Elovl6*$^{-/-}$).

Pancreases were excised, fixed in 10% neutrall buffered formalin, embedded in paraffin and cut into 4-micrometer-thick sections. The author stained the sections with antibodies to examine the expressions of proteins or BrdU antibody to check proliferative activity with secondary antibodies.

Isolation of islets from mice was performed by Ficoll-Conray density gradient centrifugation and hand picking. The author checked insulin secretion of these islet cells using ELISA kit.

【結果・考察　Results】

1) The author found that both *db/db* and *db/db: Elovl6-/-* mice during 6-16 weeks old show gained body weight (BW) without any significant differences. The author also found that at 40 weeks of age, *db/db* mice exhibited diabetes and BW loss, whereas *db/db: Elovl6-/-* mice sustained a gain without hyperglycemia and hyperinsulinemia.
2) The author found that in *db/db: Elovl6-/-* mice, increased secretin of insulin was observed by OGTT, whereas insulin sensitivity did not change compared to *db/db* mice by ITT.
3) The author found that liver weight, heaptic triglyceride, total cholesterol, and alanine transaminase levels were higher in *db/db: Elovl6-/-* mice than *db/db* mice. And the author found the dramaric increase in lipid droplets in *db/db: Elovl6-/-* mice compared to *db/db* mice by histological analysis.
4) The author did hepatic gene analysis and found that increased expression of glucokinase and stearoyl-CoA desaturase 1 and decreased expression of glucose-6-phosphase in *db/db: Elovl6-/-* mice compared to *db/db* mice.
5) The author found that in *db/db: Elovl6-/-* mice, the number and size of islets were greater, resulting in enlarged size of islets and increased beta-cell mass compared to *db/db* mice.
6) The author found that islet hyperplasia in *db/db: Elovl6-/-* mice was a consequence of increased proliferation and reduced apoptosis of beta-cells.
7) The author found that insulin content was higher in *db/db: Elovl6-/-* mice than *db/db* mice.
8) The author found that there was a marked reduction in oleate composition of *db/db: Elovl6-/-* islets compared to *db/db* islets.
9) The author found that Elovl6 deficiency significantly decreased the expression of prionflammatory genes, such as CD68, TNF-alpha, IL-1beta, CCL2, CCR2, CCL21a, Glycam1, and Saa3 in both *db/+* and *db/db* islets.
10) The author found the cellular oleate content could be a determinant of *Elovl6*-mediated beta-cell function and the FA composition of islets in *db/db: Elovl6-/-* mice was favorable for the protection of beta-cells in *db/db* mice.

## 審査の要旨
## Abstract of assessment result

【批評　General Comments】

The author clearly demonstrated that *db/db:Elovl6*$^{-/-}$ mice had improved glucose tolerance, enhanced GSIS, hyperinsulinemia, and markedly increased β-cell mass associated with increased proliferation and decreased apoptosis compared to *db/db* mice. In addition, the author clarified the molecular mechanisms underlying these phenotypic changes in *db/db;Elovl6*$^{-/-}$ mice, that involve decreased expression of islet proinflammatory genes and attenuated islet inflammation accompanied with decreased islet oleate and TG levels. Of note, the author's findings indicated that *Elovl6*-mediated modulation of intracellular FA metabolism in β cells was essential in preventing the toxic effects of FAs and preserving proper β-cell function, suggesting that limiting *Elovl6* expression in individuals during early diabetes or in those with metabolic syndrome might be beneficial for T2D prevention and treatment.

【最終試験の結果　Assessment】

The final examination committee conducted a meeting as a final examination on May 31, 2017. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結果　Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.